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Rilonacept

Prop INN; USAN

IL-1 Inhibitor
Treatment of Autoimmune Diseases
Treatment of Inflammatory Disorders

IL-1 Trap

Interleukin 1 receptor accessory protein (human extracellular domain fragment) fusion protein with type I interleukin 1 receptor (human extracellular domain fragment) fusion protein with immunoglobulin G_1 (human Fc fragment), homodimer [653-Glycine][human interleukin-1 receptor accessory protein-(1-339)-peptide (extracellular domain fragment) fusion protein with human type 1 interleukin-1 receptor-(5-316)-peptide (extracellular domain fragment) fusion protein with human immunoglobulin G_1-(229 *C*-terminal residues)-peptide (Fc fragment)], (659-659':662-662')-bisdisulfide dimer

CAS: 501081-76-1

EN: 298149

Abstract

The proinflammatory cytokine interleukin-1 (IL-1) has been implicated as playing a pathogenic role in several systemic inflammatory diseases, and thus neutralization of IL-1 activity has emerged as an important therapeutic strategy to alleviate the symptoms of inflammatory and/or immune-mediated diseases. Several IL-1-blocking mechanisms are available and include the recombinant IL-1 receptor antagonist (IL-1Ra) anakinra (Kineret®), anti-IL-1β monoclonal antibodies, antibodies to type I IL-1 receptor (IL-1RI) and IL-1R accessory protein (IL-1RAcP), soluble forms of IL-1RAcP, inhibitors of caspase-1 and soluble IL-1 receptors. However, efficacy and potency can be limited due to the need for daily administration, induction of immune responses and/or possible enhancement rather than blockade of cytokine activity. Another novel approach for blocking IL-1 activity was developed and involves the use of an IL-1-specific cytokine trap. Rilonacept is one such molecule that consists of the extracellular domains of the IL-1RAcP and the human IL-1RI fused to the Fc portion of human IgG_1. Rilonacept was shown to bind IL-1β and IL-1α with high affinity and potently inhibit IL-1 activity both *in vitro* and *in vivo*. Rilonacept was chosen for further development and is currently undergoing clinical trials for the treatment of cryopyrin-associated periodic syndromes (CAPS) and other inflammatory conditions.

Background

Cytokines are small, nonstructural proteins with molecular weights ranging from 8 to 40,000 which all nucleated cells can synthesize and respond to. They regulate several essential biological processes, including acute gene expression, cell proliferation and chronic inflammation. Cytokines can be broadly classified into antiinflammatory and proinflammatory, although many are pleiotropic in nature, and depending on the response, may exert both anti- and proinflammatory activity. The antiinflammatory cytokines, such as the interleukins IL-4, IL-10 and IL-13, reduce inflammation and promote healing, while proinflammatory cytokines, such as interferon gamma (IFN-γ), tumor necrosis factor (TNF), IL-1, IL-2, IL-6, IL-15, IL-17 and IL-18, cause inflammation and complicate disease. Targeting the proinflammatory cytokines represents an attractive strategy for a number of diseases. Three of the most validated cytokine targets are IL-1, IL-4 and IL-6, which have been shown to be implicated in rheumatoid arthritis, inflammatory bowel disease (IBD), congestive heart failure, osteoporosis, cachexia and cancer (1-3).

IL-1 activity in particular has been linked to many systemic inflammatory diseases which are characterized by recurrent fevers, leukocytosis, anemia and elevated acute-phase proteins. A model for IL-1-mediated systemic inflammation has been proposed (Fig. 1). Under conditions of noxious stimulation, monocytes or macrophages adhere to endothelial or serosal surfaces that express the IL-1 receptor type I (IL-1RI), where they begin to synthesize the inactive IL-1β precursor. IL-1β-converting enzyme, also known as caspase-1, cleaves the inactive precursor, releasing the active IL-1β, which subsequently enters the circulation. It in turn acts on bone marrow, where it is involved in various processes of hematopoiesis such as the induction of the proliferation of pluripotent bone marrow progenitor cells and the release of neutrophils. It also activates the serotonergic system and functions as an endogenous pyrogen, inducing sig-

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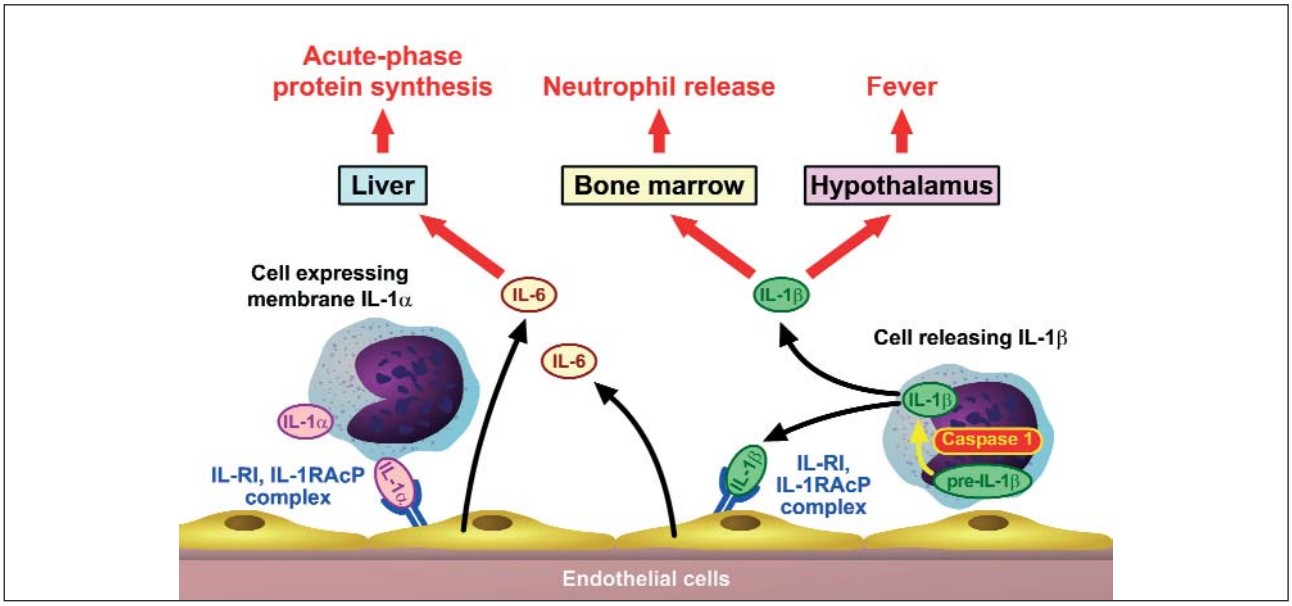

Fig. 1. Role of IL-1 in systemic and local inflammation. Activated monocytes or macrophages adhere to endothelial/serosal surfaces and synthesize inactive pre-IL-1β, which is subsequently cleaved by caspase-1 (IL-1β-converting enzyme) to form active IL-1β. Active IL-1β enters the circulation and reaches the bone marrow, where it stimulates neutrophil release, and the hypothalamus, where it induces fever. The actions of IL-1β are mediated via binding to the IL-1 receptor type I (IL-1RI) expressed on endothelial and serosal cell surfaces and complexed with IL-1R accessory protein (IL-1RAcP). IL-1β also stimulates inflammatory responses in adjacent endothelial tissue, including stimulation of the production of adhesion molecules, chemokines and IL-6. IL-6 enters the circulation and eventually reaches the liver, where it stimulates acute-phase protein synthesis. Membrane-bound IL-1α is also shown. It is functionally comparable to IL-1β, binding to and activating the IL-1RAI/IL-1RIcP receptor complex to produce similar inflammatory responses.

nificant elevations in body temperature by causing the release of prostaglandins in the thermoregulatory center of the hypothalamus. In addition, inflammatory processes may be activated by binding to IL-1RI on adjacent endothelial cells. Both soluble IL-1β and membrane-bound IL-1α bind with low affinity to IL-1RI on adjacent endothelial cells, which results in recruitment of a second receptor component, the IL-1R accessory protein (IL-1RAcP). Together, these two receptors bind the cytokine with higher affinity than either receptor component alone. Moreover, docking of IL-1RAcP is required for signal reduction. Activation of the complex and the resultant signaling consequently causes production of adhesion molecules, chemokines and IL-6. Circulating IL-6 levels increase, eventually reaching the liver where acute-phase protein synthesis is induced. Thus, neutralization of IL-1 activity has emerged as an important therapeutic strategy to alleviate the symptoms of inflammatory and/or immune-mediated diseases. Several mechanisms have been reported that can potentially reduce IL-1 activity. These include IL-1 receptor antagonists (IL-1Ra) such as anakinra (Kineret®), anti-IL-1β monoclonal antibodies, anti-IL-1RI antibodies, anti-IL-1RAcP antibodies, soluble forms of IL-1RAcP, inhibitors of caspase-1 and soluble IL-1 receptors. IL-1-blocking agents currently under active development are shown in Table I. Unfortunately, the efficacy and potency of these agents can be limited. Daily administration may be required due to rapid clearance and problems with receptor occupancy issues. Moreover, immune responses may be induced and, if an individual soluble receptor is used, activity may be enhanced rather than inhibited since IL-1 acts via a multicomponent receptor system (4-6).

Another novel approach for blocking IL-1 activity has been described and involves using molecules known as cytokine traps. Cytokine traps are a fusion between the Fc region of immunoglobulin (Ig) G_1 and extracellular domains of cytokine receptor components involved in cytokine binding. Rilonacept is an IL-1 trap comprised of the extracellular domains of IL-1RAcP and human IL-1RI fused to the Fc portion of human IgG_1. Rilonacept was shown to bind IL-1β and IL-1α with high affinity and to potently inhibit IL-1 activity both *in vitro* and *in vivo*. Rilonacept was chosen for further development as an anti-IL-1 agent for the treatment of several inflammatory and immune-mediate diseases and is currently in pivotal clinical trials for cryopyrin (*CIAS1*)-associated periodic syndromes (CAPS), for which both orphan drug status and fast track designation have been awarded by the FDA (7-9).

Preclinical Pharmacology

Rilonacept was shown to potently inhibit IL-1β (4 pM)-stimulated IL-6 production from the human MRC5 fibroblast cell line, with an IC_{50} value of approximately 2 pM and an estimated K_D value of about 1 pM. In comparison, IL-1Ra was less effective (IC_{50} about 70 pM) and the sol-

Table I: IL-1–blocking agents currently under active development for a variety of indications (from Prous Science Integrity®).

Drug	Mechanism of action	Source	Condition	Phase
ACZ-885	Anti-IL-1β monoclonal antibody	Novartis	Muckle-Wells syndrome	III
Rilonacept	IL-1 trap	Regeneron	Autoimmune and inflammatory diseases	II-III
AMG-108	Anti-IL-1β monoclonal antibody	Amgen	Rheumatoid arthritis	II
ITF-2357	IL-1β production inhibitor	Italfarmaco	Autoinflammatory syndromes	II
Ajulemic acid (IP-751)	IL-1β inhibitor	Indevus	Neuropathic pain, interstitial cystitis	I-II
AN-2728	IL-1β release inhibitor	Anacor	Psoriasis	I
DOM-0400	Anti-IL-1 domain antibody	Domantis (GlaxoSmithKline)	Rheumatoid arthritis, chronic obstructive pulmonary disease and osteoarthritis	Preclinical

uble monomeric ectodomains of IL-1RI or IL-1RII, which have relatively low binding affinities (K_D = 1-3 nM and 500 pM, respectively), were weak blockers of IL-1β. Rilonacept was also demonstrated to block IL-1α with high affinity (K_D about 3 pM), 100 times greater that that of the soluble monomeric component receptor IL-1RI. Further binding experiments with rilonacept in which varying concentrations of the trap were mixed with IL-1β revealed an IC_{50} value of 6.5 pM in the presence of 10 pM IL-1β, which corresponds to a K_D value of 1.5 pM; rilonacept had no effect on IL-4 responses. Rilonacept bound about 23-fold more tightly than IL-1Ra. The IL-1RAcP component of rilonacept was shown to be required for the high affinity of the agent for IL-1β in experiments using a monoclonal antibody against IL-1RAcP (U10B3) to prevent interaction of this component with IL-1β (7).

Rilonacept also blocked the ability of human IL-1β (0.6 μg/kg) to stimulate IL-6 secretion *in vivo* when administered s.c. (0.51 mg/kg 24 h before IL-1β) to C57BL/6 mice. The rapid increase in serum IL-6 seen following IL-1β treatment was blocked in rilonacept-treated animals. Rilonacept-induced blockade was prolonged, since a single dose also blocked serum IL-6 peaks following a second injection of IL-1β 24 h later. IL-1β induction of IL-6 secretion was not blocked in mice treated with similar or 15-fold higher doses of IL-1Ra (7).

A murine version of rilonacept (10 or 31 mg/kg 3 times/week for 8 injections starting on day 30 after collagen immunization) effectively blocked the development of arthritic joints and hindlimb bone erosion in a mouse (DBA/1Lac) collagen-induced arthritis model (7).

Rilonacept protected against IL-1β-induced functional suppression and cytokine-mediated cytotoxicity in isolated rat pancreatic islets *in vitro*. Treatment at a rilanocept:IL-1β (150 pM) ratio of 10:1 or 100:1 blocked IL-1β-mediated inhibition of insulin secretion and glucose oxidation rate and enhancement in nitrite accumulation (*i.e.*, marker of nitric oxide production). Treatment at 100:1 significantly inhibited the increase in islet cell death seen with concomitant IL-1β, TNF-α and IFN-γ (10).

Expression of the IL-1β gene was shown to be increased over 20-fold in a mouse atherosclerosis model ($ApoE^{-/-}$ mice subjected to carotid artery ligation), suggesting that this cytokine plays a crucial role in arterial inflammation. This hypothesis was confirmed when a murine version of rilonacept was administered to these mice. Prophylactic treatment with the agent (s.c. 3 times/week for 4 weeks or via hydrodynamic DNA transfection prior to ligation) markedly and dose-dependently decreased the severity of complex plaque formation, with a significant reduction in lesion area of more than 85% observed. The doses of the murine IL-1 trap used in this model were 30-fold lower than those required in a mouse rheumatoid arthritis model (11, 12).

Pharmacokinetics and Metabolism

The pharmacokinetics of s.c. and i.v. rilonacept (3 mg/kg) were examined in cynomolgus monkeys, with results showing that the agent persists in the circulation for many days. C_{max} and terminal $t_{1/2}$ values obtained were 13.1 μg/ml and 67 h, respectively, and the bioavailability was 70% (7).

A randomized, placebo-controlled, double-blind, single-dose phase I study conducted in 20 patients with rheumatoid arthritis examined the pharmacokinetics of rilonacept (50, 100, 200 or 400 μg/kg s.c.). Dose-proportional pharmacokinetics were obtained. C_{max} values for the 4 doses were 218, 300, 747 and 1896 ng/ml, respectively, and terminal $t_{1/2}$ values were 128, 162, 214 and 182 h, respectively (13).

Clinical Studies

IL-1 is suspected to mediate the inflammatory responses leading to an increase in the risk for cardiovascular events. A placebo-controlled study conducted in 107 healthy volunteers examined the effect of a single rilonacept dose on serum levels of the cardiovascular risk factor marker C-reactive protein (CRP) over 6 weeks. Treatment with the agent significantly decreased serum CRP levels to a median of about 56% on day 5; no decrease were observed in subjects receiving the placebo. Moreover, those subjects who had elevated CRP at baseline (> 2.87 mg/l) exhibited a decrease of approximately 72% in CRP levels with treatment as compared to an increase of approximately 8% seen on placebo. CRP levels were suppressed for up to 1 month (14).

Another randomized, placebo-controlled, double-blind, single-dose phase I study in 107 patients with

rheumatoid arthritis examined the safety and efficacy of rilonacept (50, 100, 200, 400 or 800 μg/kg s.c. for 6 weeks). Patients were allowed concomitant methotrexate or prednisone treatment. The agent was well tolerated, with no serious adverse events. The incidence of adverse events was similar in both treatment and placebo groups. The most common adverse event was short-lasting stinging at the injection site. No anti-rilonacept antibodies were detected in any of the patients over the 9-week observation period. Pharmacokinetic analysis revealed a C_{max} of 3.5 μg/ml at the highest dose, which increased to 10.8 μg/ml over the 6-week treatment period, and a $t_{1/2}$ value of 7.5 days for the two higher doses, thus supporting weekly dosing. Dose-dependent reductions in swollen and tender joint counts and serum CRP levels were observed. A large number of patients receiving the highest dose exhibited improvements in the American College of Rheumatology ACR20 response criteria over the treatment period (15). The results from this and several of the following studies are depicted in Table II.

The safety and efficacy of rilonacept (25, 50 or 100 mg by weekly s.c. injections) were evaluated in a 12-week, randomized, multicenter, placebo-controlled phase II trial in 201 subjects with moderate to severe rheumatoid arthritis who had failed at least one prior disease-modifying antirheumatic drug (DMARD). The agent was well tolerated, with no significant infectious complications seen. The most common adverse event was burning at the injection site (34% in the placebo and rilonacept 100 mg groups). No significant differences in the primary endpoint of ACR20 response at 12 weeks were observed between treatment groups and placebo (46.0% on rilonacept 100 mg *vs.* 30.9% on placebo). However, significant improvements in Disease Activity Score (DAS28) were obtained on the highest dose compared to placebo, with significant effects first observed at 1 week of treatment (–0.55 *vs.* –0.29) and continuing to the end of treatment (–1.121 *vs.* –0.702). Moreover, significant differences were observed in DAS good and moderate responders between the 100-mg and placebo groups (46% *vs.* 26%). Baseline levels of IL-1, IL-1Ra, IL-1/IL-1Ra ratio, serum amyloid A (SAA) or CRP were not predictive of response to therapy, although the relationship between baseline IL-6 levels and response approached significance (p = 0.7). Treatment

Table II: Clinical studies of rilonacept (from Prous Science Integrity®).

Indication	Design	Treatments	n	Conclusions/Objectives	Ref.
Arthritis, rheumatoid	Randomized Double-blind Multicenter	Rilonacept, 50 μg/kg s.c. 1x/wk x 6 wks (n=5) Rilonacept, 100 μg/kg s.c. 1x/wk x 6 wks (n=5) Rilonacept, 200 μg/kg s.c. 1x/wk x 6 wks (n=18) Rilonacept, 400 μg/kg s.c. 1x/wk x 6 wks (n=16) Rilonacept, 800 μg/kg s.c. 1x/wk x 6 wks (n=18) Placebo (n=20)	82	Rilonacept was well tolerated and appeared to improve ACR criteria in patients with active rheumatoid arthritis	15
Arthritis, rheumatoid	Randomized Multicenter	Rilonacept, 25 mg s.c. 1x/wk x 12 wks Rilonacept, 50 mg s.c. 1x/wk x 12 wks Rilonacept, 100 mg s.c. 1x/wk x 12 wks Placebo	201	Rilonacept significantly decreased biochemical markers of inflammation and joint tissue breakdown in patients with rheumatoid arthritis	17
Arthritis, rheumatoid (juvenile)	Randomized Double-blind Multicenter	Rilonacept, 2.2 mg/kg s.c. x 4 wks Placebo	11	Preliminary results suggested that rilonacept exhibited clinical and biological activity in patients with systemic juvenile idiopathic arthritis	19
Cold auto-inflammatory syndrome, Muckle-Wells syndrome	Open	Rilonacept, 100 mg s.c. o.d. x 3 → [upon flare] 100 mg s.c. o.d. x 3 → 100 mg/wk x 1 y	4	All 4 patients with cryopyrin-associated periodic syndromes showed immediate response to rilonacept therapy, with a maximum response at day 9 and improvement in laboratory values and physician and patient assessments. All patients developed a flare at a median of 21 days after the first doses, but reinstitution of therapy resulted in another immediate response. No patients experienced significant adverse events or injection-site reactions	21, 22
Cold auto-inflammatory syndrome, Muckle-Wells syndrome	Randomized Double-blind	Rilonacept, 160 mg s.c. x 6 wks Rilonacept, 160 mg s.c. x 9 wks Placebo	47	Rilonacept was associated with notable reductions in signs and symptoms in patients with familial cold autoinflammatory syndrome and Muckle-Wells syndrome	23
Atherosclerosis	Randomized Double-blind	Rilonacept s.c. 1x/2 wks Placebo	60	A phase II study will evaluate the efficacy of rilonacept in improving arterial function in patients with atherosclerosis	26

dose-dependently reduced CRP, α_1-acid glycoprotein (AGP), erythrocyte sedimentation rate (ESR), IL-6 and SAA levels. Those patients who achieved an ACR50 response with treatment had significantly lower baseline levels of IL-6 and greater reductions in serum SAA and serum matrix metalloproteinase-1 (MMP-1) as compared to nonresponders (16, 17).

Preliminary data from 11 patients enrolled in the open-label extension phase of a randomized, double-blind, placebo-controlled study conducted in patients with systemic juvenile idiopathic arthritis (SJIA; mean disease duration = 3.8 years) revealed biological activity for rilonacept (2.2 mg/kg s.c. for 4 weeks). Patients included in the analysis received a minimum of 2 weeks of open-label therapy. Improvements were noted with treatment in all 6 ACR Pediatric (Ped) core set variables analyzed. ACR Ped 30, 50 and 70 responses were 77.8%, 55.6% and 22.2%, respectively, after 2 weeks. ACR ped 50 and 70 at 4 weeks of open-label treatment were 77.8% and 44.4%, respectively. Those patients who had fever or rash at baseline had complete resolution with treatment. Improvements were also observed in white blood cell and platelet counts and hemoglobin levels. In addition, D-dimer was markedly decreased and the increased CRP levels were almost normalized. Patients who did not adequately respond to previous anakinra (IL-1Ra) therapy exhibited a response to rilonacept (18, 19).

Preliminary data were presented from 2 patients with adult-onset Still's disease (AOSD) who had failed etanercept or infliximab combined with methotrexate and high-dose corticosteroids and who were enrolled in a pilot trial examining the efficacy and safety of rilonacept (loading regimen of 100 mg/day s.c. for 3 days followed by 100-320 mg/day in an extension phase) in autoinflammatory diseases, including *CIAS1*-associated diseases, AOSD, colchicine-resistant familial Mediterranean fever (FMF), familial cold autoinflammatory syndrome (FCAS) and Muckle-Wells syndrome (MWS). Treatment was generally well tolerated and no serious adverse events were reported. Symptomatic improvement was reported by both patients after starting rilonacept treatment, although differential responses were noted. Daily diary scores for signs and symptoms for 1 patient who had more prominent systemic symptoms decreased between days 0 and 10 from 8.3 to 3.3. The patient also experienced decreases in acute-phase reactants (ESR decreased from 67 mm/h to 45 mm/h, CRP decreased from 7.13 mg/dl to 2.54 mg/dl and SAA decreased from 171 mg/l to 22 mg/l). Although signs and symptoms returned at the end of the 3-day dosing regimen, rapid responses occurred again with initiation of a second loading regimen. Daily diary scores for the second patient who had more prominent polyarthritis were 11.9 and 9.6 on days 0 and 10, respectively, and acute-phase reactant scores on these respective days were 126 and 108 mm/h for ESR, 11.9 and 9.82 mg/dl for CRP and 712 and 1010 mg/l for SAA. The dose of rilonacept was subsequently increased in this patient to 360 mg every week; the daily diary score decreased by 2 at 9 months, but only minimal improvements were seen in inflammatory markers (54 mm/h, 7.65 mg/dl and 774 mg/l for ESR, CRP and SAA, respectively) (20).

Immediate clinical and laboratory improvements were observed with rilonacept therapy (loading regimen of 100 mg/day s.c. for 3 days followed by 100 mg/week for 1 year in an extension phase) in 4 patients with FCAS/MWS enrolled in the above pilot study. All patients carried mutations in the cryopyrin-encoding *CIAS1* gene which is associated with IL-1β upregulation, NF-κB modulation and apoptosis. No significant adverse events or injection-site reactions were reported. A maximum response to therapy was seen on day 9, with flares occurring in all patients at a median of 21 days. Daily diary scores were significantly reduced after therapy onset (from 6.06 to 1.67), but increased again with flares. Initiation of a second loading regimen produced rapid responses. Significant reductions were also observed in CRP (from 7.28 mg/dl to 0.72 mg/dl), ESR (from 56.67 mm/h to 24 mm/h) and patients' global visual analog scale (VAS) scores (from 5.2 cm to 1.1 cm); SAA and physician VAS scores also decreased, but results did not reach significance (21, 22).

The safety and efficacy of rilonacept (160 mg/week s.c.) were examined in a randomized, double-blind, placebo-controlled phase III study in 47 patients with FCAS/MWS. The study involved a 6-week treatment comparison phase and a second phase of single-blind rilonacept treatment followed by a 9-week randomized withdrawal comparison phase. No serious adverse events were reported, although more injection-site reactions, the majority of which were mild, and mild to moderate upper respiratory tract infections were observed with rilonacept treatment. Substantial decreases in signs and symptoms were observed during the first 6-week treatment phase. Significant mean changes in DAS (rash, fever/chills, joint pain, eye redness/pain and fatigue) of 85% and significant decreases in SAA (93% *vs.* 0%) were observed at the end of the first treatment phase as compared to placebo. During the second withdrawal phase, patients treated with placebo had a gradual return of disease activity (23).

Rilonacept continues to undergo phase II and III development for treatment of inflammatory and autoimmune diseases, including neonatal onset multisystem inflammatory disease, FCAS, MWS, FMF and AOSD, as well as atherosclerosis (24-26).

Source

Regeneron Pharmaceuticals, Inc. (US).

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